‘Intolerance of Uncertainty’ mediates the relationship between social profile and anxiety in both Williams Syndrome and autism

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Abstract

Anxiety is the most significant mental health concern for both Williams syndrome (WS) and autism. Whilst WS and autism are characterised by some syndrome-specific social differences, less is known about cross-syndrome profiles of anxiety symptoms. Previous research has shown that Intolerance of Uncertainty (IU) is a core mechanism of anxiety maintenance for clinically anxious populations and for autistic children, adolescents, and adults. The only published study in this area for WS (Uljarević et al., 2018) has shown some similar patterns – with an added emphasis on the role of sensory sensitivities -- in a sample of older teens and adults (mean age =24), with the authors highlighting the need for younger samples to consider developmental influences. Here we report a cross-syndrome, cross-sectional mediation analyses of children diagnosed with WS or autism, including data from parent surveys of 90 children with WS (n=48) or autism (n=42). Group differences showed higher trait levels on all measures for the autism group. Importantly, the relationship between social profile and anxiety was fully mediated by IU level for both groups. This suggests possible similar core mechanisms underlying anxiety in these conditions, and the possibility of generalised intervention approaches especially related to managing distress related to uncertainty in multiple contexts.

Lay Summary

Autism and Williams Syndrome share some similarities in social profile and also in anxiety traits, but there are also some key differences as well. Comparing them side-by-side at the same time improved identification of ways to reduce feelings of anxiety. We found that the intolerance of uncertainty affected the relationship between social profile and anxiety in the same way for young children diagnosed with autism or Williams Syndrome, meaning that intervention approaches could be similar for both.

Keywords: Williams Syndrome; Autism; Anxiety; Intolerance of Uncertainty; social profile; social function; children

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Capitalising on the strengths of a cross-syndrome approach to developmental disorders allows the consideration of syndrome-specific models and signatures of cognition, behaviour, or psychopathology (Rodgers et al., 2012). As an illustration, by utilising this approach it is possible to ask whether our theories of atypical social profile in autism are syndrome-specific, and thus reflect on the implications for diagnosis, theory development, and intervention. The nature of both similarities and subtle syndrome-specific differences amongst autism spectrum disorder (hereafter, autism) and WS makes them ‘model syndromes’ for cross-syndrome comparisons (Asada & Itakura, 2012; Helen Tager-Flusberg et al., 2006). In the current research, we capitalise on a cross-syndrome methodology to understand the role of an ‘intolerance of uncertainty’ (IU) in mediating the relationship between social profile and anxiety in autism compared to Williams syndrome (WS). This methodological approach will aid both theory development and intervention design by elucidating potential syndrome-specific signatures of social profile and anxiety and their relationship to IU. Subsequently, interventions and support could be adapted to act upon different mechanisms across these conditions.

Both autism and WS include substantial heterogeneity across individuals, including differences in style of social motivation and in level of anxiety. On the whole, previous studies have characterized atypical social motivation in WS as an increased drive toward social engagement (e.g., Jones et al., 2000; Vivanti, Hocking, Fanning, & Dissanayake, 2016) and increased attention to people and faces (Riby & Hancock, 2008, 2009); additionally, interactions and social approach in WS are not modulated as expected by degree of the familiarity with a partner (Lough et al., 2016; Riby et al., 2014). This increased social drive occurs in parallel with mild-to-moderate learning difficulties (Searcy et al., 2004) and

difficulties making socio-cognitive judgements (Tager-Flusberg & Sullivan, 2000), meaning that this constellation of issues can lead to heightened social vulnerability (Riby et al., 2017). So although many individuals with WS have high degrees of social motivation (with heterogeneity; Little et al., 2013), they tend to lack sophisticated social expertise.

Desire for social interaction can be variable across autistic individuals: some show active motivation to affiliate with others and work hard to overcome difficulty understanding normative social expectations (Jaswal & Akhtar, 2019; Livingston et al., 2019), while others show atypically reduced social motivation and reduced attention to socially relevant information from faces (Klin et al., 2002; Riby & Hancock, 2009) which may be associated with confusion when making socio-cognitive judgments of others (c.f., Leekam, 2016), and which ultimately impacts upon daily social interaction. Atypical social attention and social information processing can occur together in autism (Chevallier et al., 2012) which can be associated with poor adult outcomes related to social integration and independence (see Magiati, Tay, & Howlin, 2014 for a review).

It is well established that WS and autism are each associated with a heightened risk of anxiety compared to the general population (Rodgers et al., 2012; Royston et al., 2016; South & Rodgers, 2017). For both these conditions, anxiety has been identified as the most significant mental health challenge (Simonoff et al., 2008; Stinton et al., 2012). Understanding the mechanisms underlying anxiety in these groups is particularly important for theory and intervention.

Research consistently demonstrates an association between lower social motivation and higher levels of anxiety in both autism (Factor et al., 2016; South et al., 2017; Spain et al., 2018; Swain et al., 2015; White et al., 2014) and WS (Barak & Feng, 2016; McGrath et al., 2016; Riby et al., 2014), although caution is necessary for implying that social motivation drives anxiety, as increased anxiety could easily depress social motivation. However, there

has been less work with WS samples regarding the underlying mechanisms that drive such links. One goal of this study was to examine whether Williams Syndrome and autism illustrate the same broad sort of differences in profiles for anxiety as they do for social development.

One mechanism for anxiety that is emerging in autism research is Intolerance of Uncertainty (IU; Boulter, Freeston, South, & Rodgers, 2014; Keefer et al., 2016; South & Rodgers, 2017). IU is a transdiagnostic concept defined as *"the dispositional tendency to experience fear of the unknown"* (Bomyea et al., 2015). IU is not unique to anxiety in autism, as it is believed to play a role as a crucial cognitive mechanism in other clinical conditions including generalised anxiety disorder (Bomyea et al., 2015; Dugas, Gagnon, Ladouceur, & Freeston, 1998) and major depression (Einstein, 2014). IU may play a particularly important role in the maintenance of high anxiety levels (e.g. Dugas et al., 2007) and interventions that target IU have been utilised in clinical anxiety disorders (Dugas et al., 2003, 2010; Dugas & Ladouceur, 2000) and recently for individuals with autism (Rodgers, Wigham, et al., 2016).

Clinical experience, building on previous research (Rodgers et al., 2012), likewise suggests the relevance of studying uncertainty in WS. To date, we know of one published short report that addresses IU in WS with a focus on the interaction of IU and sensory processing (Uljarević et al., 2018). Their sample consisted of parents/guardians of 32 WS individuals ages 14-43 (mean 24.76 years) and measured parent-reported anxiety, IU, sensory processing, and social profile. They reported that sensory sensitivity and IU, but not social communication scores, uniquely predicted anxiety scores in the WS sample. This matches previous findings in autism research and argues that support and interventions for IU may be helpful for WS the same as they may be for autism (Keefer et al., 2016; Rodgers, Hodgson, et al., 2016). The authors note, however, that because they studied adults it is difficult to comment how the relative contribution of sensory processing vis-à-vis IU to anxiety may

change over development. The study reported in this paper adds to the findings of Uljarević et al. in three key areas: a) we report data from a much younger sample (mean age = 10.4); b) includes a cross-syndrome sample collected with the same measures at the same time; c) explores the role of IU in mediating the relationship between social profile and anxiety. Unlike the Uljarević et al. study, we did not include a measure of sensory sensitivity.

There are several possible reasons why IU might account for links to anxiety in autism and WS (see Vasa et al., 2018). For example, cognitive flexibility may be associated with expression of anxiety-related behaviours in autism (Bos et al., 2019; Faja & Nelson Darling, 2019 and WS (Ng-Cordell et al., 2018). Cognitive flexibility seems to be related to response inhibition which may contribute to persistent worrisome thoughts in anxiety and is also related to social difficulties and repetitive behaviours in autism (Schmitt et al., 2019). Inflexible thinking may likewise contribute to difficulties managing multiple possible outcomes thus exacerbating intolerance of uncertainty (Rodgers, Hodgson, et al., 2016; South et al., 2019). Atypical sensory processing seen in both autism (Green & Ben-Sasson, 2010; Wigham et al., 2014) and WS (Janes et al., 2014; Riby et al., 2013; Uljarević et al., 2018), may heighten feelings of uncertainty; alternatively, elevated levels of anxiety could underlie frequent hypervigilance that leads to hyper-sensory processing (Green & Ben-Sasson, 2010; Top Jr. et al., 2016).

This study first hypothesises that social profile and anxiety are atypical in both autism and WS, even though the nature of the atypicality is syndrome-specific and within-syndrome heterogeneity is evident in both groups. The study then hypothesises that IU plays a mediating role in the relationship between social profile and anxiety in autism (replicating Boulter et al., 2014) and extends to new evidence hypothesising that this same relationship exists in WS. At present it is not possible to hypothesise whether the strength of the relationship will vary by syndrome.

Method

Participants

Participants were the parents of 90 individuals with WS or autism aged between 4- and 18-years in the UK and Ireland. Eighty of the questionnaires were completed by mothers, three by both parents together, and seven by fathers. All parents were recruited through existing research links for our research group and support charities for individuals with these developmental conditions and their families (including the Williams Syndrome Foundation UK and the Williams Syndrome Association of Ireland). Data were first excluded for five children who had a dual diagnosis of WS and autism, and for one whose official diagnosis was not yet completed. The final sample included parents of 48 children with WS (28 girls; mean age 9 years 10 months) and parents of 42 children with autism (3 girls; mean age 11 years 1 month). There was not a significant between-group difference in age, $t = 1.44$, $p = .152$.

As this was an online survey, we did not conduct diagnostic evaluations or genetic tests. However, all respondents confirmed that their child had previously been formally diagnosed with either WS or autism. For the same reasons, we did not have a formal measure of cognitive performance. Data regarding school placement were collected and results are as follows: for the WS group, 18 children (38%) were in mainstream school placements alone; 7 (15%) were in mainstream placements with some additional special education services; 19 (40%) were in special education needs (SEN) placements, and four children were not in school; for the autism group, 22 children (52%) were in mainstream school placements alone; 4 (10%) were in mainstream placements with some additional special education services; 15 (38%) were in SEN placements, and one child was not in school. Thus, children in both samples spanned a full range of service provision.

Materials

Parents completed a battery of online questionnaires in their own time, which measured aspects of social behaviour, anxiety and intolerance to uncertainty.

- Social Responsiveness Scale - Second Edition (SRS-2; Constantino & Gruber, 2012). The SRS-2 is a 65-item, 4-point Likert scale parent-report measure that characterizes individual social profiles across a range of domains. The measure is reported to show high internal consistency (Chronbach $\alpha = .95$; Constantino & Gruber, 2012).
- Spence Children's Anxiety Scale – Parent Version (SCAS; Spence, 1998). The SCAS is a 38-item parent-report questionnaire using a 4-point Likert scale. The SCAS maps onto DSM-IV criteria for childhood anxiety disorders and has been widely used as a parent-reported anxiety measure for individuals with autism and WS (e.g., Magiati et al., 2017; Riby et al., 2014). The SCAS is reported to have good internal consistency (Cronbach's $\alpha = .92$; Spence, Barrett, & Turner, 2003). Although there is no formal clinical cut-off, a total score ≥ 24 indicates clinically significant anxiety (one standard deviation above the mean in a community sample; Nauta et al., 2004) and this cut-off has been used in studies involving individuals with autism and WS (e.g.; Riby et al., 2014; Rodgers et al., 2012).
- Intolerance of Uncertainty Scale, Parent Report Short Form (IUS-12; Walker, 2009). This short version of the IUS includes 12 items in a 5-point Likert-scale format, related to the consequences for child behaviour in situations of uncertainty (e.g., "Feeling unsure stops my child from doing most things"). Previous studies have shown good reliability and validity for the IUS-12 in autism samples (Boulter et al., 2014; Stephenson et al., 2016; Wigham et al., 2014).

A fourth completed questionnaire, the Anxiety Scale for Children-Autism Spectrum Disorder Parent Report (Rodgers et al., 2016) has significant overlap with the construct of uncertainty measured by the IUS-12, including shared core items, and thus was not included in these analyses. Parents also completed the Behavior Assessment System for Children-3rd Edition, which is being reported as part of a separate study and was not analyzed here.

Procedure

All parent participants provided informed consent prior to participation. Parents were asked to complete the questionnaires as delivered online through Bristol Online Survey software (University of Bristol, 2017; https://www.onlinesurveys.ac.uk) in the spring of 2017. Parents were told that their responses were both anonymous and confidential and that no individual child could be identified from the data or in subsequent publications. At the end of the questionnaires, parents were debriefed and thanked for their time.

Results

Internal consistency measured by Cronbach's alpha was high for all measures (all αs > .94).

Descriptive data

A summary of descriptive information is depicted in Figure 1 and complete data are laid out in Table 1. Whilst there was significant heterogeneity within both groups, the average score for each group was elevated for every measure and was above the recommended cut-off scores for clinical concern for the SRS-2 and SCAS. Our data indicate that 98% of the autism group and 93% of the WS group were rated with at least 'mild' levels of clinical concern on the SRS-2. On the SCAS, 79% of the autism sample and 51% of the WS sample were reported by parents as having significantly high levels of anxiety. Although the IUS-12 has

no established cut-off scores, mean scores for both groups were also above previously-reported neurotypical comparison scores on the IUS-12 (Boulter et al., 2014: neurotypical mean = 22.39; Stephenson, Quintin, & South, 2016: neurotypical mean = 22.92).

The autism group scored significantly higher than the WS group on each measure. Sex differences were examined for the WS group, which included more equal numbers of boys and girls, and there were no between-sex differences in any variable.

[insert Figure 1 and Table 1]

Correlation analyses

Both groups demonstrated significant positive correlations between social functioning profile measured by the SRS-2, with anxiety and IU, as shown in Table 2. Age was not correlated with any measure (all *r*s <.29).

[insert Table 2]

Mediation Analyses

Meditation analyses were employed to explore the relationship between anxiety and social profile scores. All analyses were conducted using the PROCESS macro for SPSS Version 25 (Hayes, n.d.). In these models, social profile score was entered as the independent variable, intolerance of uncertainty as the mediator, and anxiety as the dependent variable. We used a bootstrapping approach to test significance of indirect effects as outlined by Preacher and Hayes (2008), which is considered appropriate for use with small sample sizes (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Estimates of indirect effects were based on 5,000 resamples and we report unstandardized coefficients and bias-corrected confidence intervals for the indirect effects. Confidence intervals for these indirect effects that do not contain zero are considered significant. The ratio of the indirect effect to the total

effect was then also explored to suggest the influence of uncertainty on the relationship between social profile and anxiety. In order to compare relationships across the autism and WS groups, separate models were run for each group.

No multivariate outliers or indicators of multicollinearity were observed. Four univariate outlying values were noted, two in each group, one each for the SRS-2 and SCAS variables in each group. We repeated analyses with these values fenced to the nearest boundaries and there were no meaningful differences in results, thus all results are reported with the full sample.

Autism Sample

The mediation model for autistic children is shown in Figure 2a. In this model, social profile score on the SRS-2 had a significant relationship with anxiety on the SCAS ($t = 3.18$, $p = .003$) and the mediator, intolerance of uncertainty ($t = 5.52$, $p < .001$). The relationship between intolerance of uncertainty and anxiety on the SCAS was also significant when controlling for social profile on the SRS-2 ($t = 3.51$, $p = < .001$). The indirect effect of the social profile on the SRS-2 on anxiety on the SCAS through intolerance of uncertainty was significant ($\beta = .29$, 95% CI [.1138, .4848]). Examining the ratio of the indirect effect to the total effect suggests that the IUS scale explains 76% of the influence of the SRS-2 social profile on anxiety. When intolerance of uncertainty was included in the model, the relationship between social profile on the SRS-2 and anxiety on the SCAS became non-significant ($t = .38$, $p = .70$).

Williams Sample

The mediation model for children with Williams Syndrome is shown in Figure 2b. In this model, social profile score on the SRS-2 had a significant relationship with anxiety on the SCAS ($t = 5.49$, $p < .001$) and the mediator, intolerance of uncertainty ($t = 7.24$, $p < .001$). The relationship between intolerance of uncertainty and anxiety on the SCAS was also

significant when controlling for social profile score on the SRS-2 (t = 5.46, p = < .001). The indirect effect of the social profile on the SRS-2 on anxiety on the SCAS through intolerance of uncertainty was significant (β = .34, 95% CI [.1963, .4836]). Examining the ratio of the indirect effect to the total effect suggests that the IUS scale explains 83% of the influence of the SRS-2 social profile on anxiety. When intolerance of uncertainty was included in the model, the relationship between social profile on the SRS-2 and anxiety on the SCAS became non-significant (t = .80, p = .43).

[insert Figure 2]

Interchange modelling to support causality

In order to test for a feedback model in which the mediator may be caused by the outcome variable, Kenny (*Mediation, accessed June 24 2020*) suggests swapping the mediator and the outcome variable to evaluate similarity of results. To do this we repeated the mediation analyses with the position of the IUS and SCAS variables in reversed positions. Results are shown in Supplemental Figure 1. Where our original models showed full mediation by IUS-12 scores for both autism and groups, these interchanged models show much lower coefficients and only partial mediation for SRS-2 scores between anxiety and uncertainty. Thus, our original hypothesized models fit the data much better than the interchanged models and support the causal mediating role of intolerance of uncertainty between social profile scores and anxiety.

Possible age effects

Our sample included children down to the age of four years old, which is the minimum age used when validating the SRS (Constantino & Gruber, 2012). However the SCAS-P was originally validated for children 8 years and older (Spence, 1998) while the IUS has been shown to work well at least down to age 7 (Comer et al., 2009). In order to check

whether our younger age made a difference, we re-tested the models (both original and interchanged) when limiting the sample only to ages 8 and older. Results, shown in Supplemental Figures 2 and 3, show no substantive differences from tests of the complete sample.

Discussion

The current data emphasise the important role of an intolerance of uncertainty (IU) in the relationship between social profiles and anxiety in both WS and autism. Our data replicated previous studies showing significant mediation effects of IU between social profile and anxiety in autism (Boulter et al., 2014; Maisel et al., 2016; Wigham et al., 2014). We likewise replicate and extend findings from Uljarević et al. (2018) regarding WS that found similar patterns of association, but our study samples a much younger age range, thus emphasising the role of IU for linking social profile and anxiety beyond the contribution of sensory processing factors. While there are syndrome-specific levels of social function, anxiety, and intolerance of uncertainty, notably overall higher trait levels in autism than in WS, traits are elevated in both groups and there is no doubt that IU is closely related to anxiety and social profile in both conditions. This is crucial for informing our understanding of behaviour and psychopathology in both conditions.

Further explication of such mechanisms is critical for effective treatment planning. There has been a proliferation of intervention studies targeting anxiety in autism over recent years with evidence for efficacy for standard and modified CBT approaches (Kerns et al., 2016; Reaven et al., 2018; Wood et al., 2015). Recent data emphasise the need for specific attention to IU, including evidence of IU as a predictor of effectiveness for anxiety treatment (Keefer et al., 2016; Rodgers, Hodgson, et al., 2016). The CUES© programme designed by Rodgers et al. included helping parents to identify signs of IU in their children, recognition of potential triggers for IU, and building strategies to specifically build tolerance for uncertainty

and pilot testing showed promising efficacy for the treatment. Our data reiterate the suggestions of Uljarević et al. (2018) that IU-based interventions should also be explored as possible routes to support anxiety needs of individuals with WS. This is now two studies which suggest that our understanding of anxiety in autism could be extrapolated to WS, indeed the mechanisms underlying the development of anxiety may be similar in these two groups. This cross-syndrome approach is especially helpful, given the rarity of WS and the difficulty in conducting RCT studies large enough to test out the efficacy of interventions specific for WS.

It is important to acknowledge potential limitations. All diagnoses for this study were reported by parents and not independently confirmed by our research team. There is potential for rater bias as all measures were completed by the same parent for each child, which could inflate correlations; however, the specificity of the model hypothesized *a priori* suggests that rater bias alone cannot explain these effects. There was a wide age range for this sample, which supports generalizability, but our sample size did not allow for extensive analyses of developmental/age contributions. Importantly, the Uljarević et al. (2018) study, which was published after data collection began for the present study, found that sensory sensitivity is an important factor to consider in these models and should be included in future studies. Indeed, a recent study from Glod et al. (2020) found that sensory profiles did not reliably distinguish children with autism from Williams Syndrome, and further looks at the role of sensory profiles in the development of intolerance of uncertainty and anxiety offer rich possibility.

Consideration of symptom measures

Differences in social communication are well documented in both autism and WS, though obviously atypical social profile is more of a hallmark of autism. Both groups scored, on the whole, in the range of concern on the SRS-2. Nonetheless, the SRS-2 manual explicitly warns against over-interpretation of findings for other developmental disorders. In

particular, we have recently highlighted elevated rates of SRS-2 scores in an anxious, but not autistic, sample of adults (South et al., 2017). In particular, items on the "social motivation" subscale of the SRS-2 primarily address social avoidance, and in South et al. the high-anxious group scored higher on this subscale than the autism group. Thus, the SRS-2 seems to capture social profile in the context of broader psychological distress including anxiety. We likewise suggest caution in the interpretation of the SCAS subscales presented in Table 1, due to the small and uneven number of items that contribute to the subscale scores and minimal data on the reliability of the individual subscale scores (Rodgers et al., 2012).

In terms of the validation and use of the IUS for individuals with intellectual disability, we can cross reference to the work of Uljarević et al. (2018) who reported good internal consistency for the IUS when completed by the parents of individuals with Williams syndrome (.94). Sáez-Suanes et al. (2020) used the IUS-12 and a similar Uncertainty Intolerance (UI) scale from the ASC-ASD (Rodgers, Wigham, et al., 2016) in a sample of 121 ID adults with a range of cognitive abilities. The authors did not report psychometric properties of these scales but uncertainty measured by the UI scale was a useful predictor of anxiety in that study. Future studies could specifically examine the validity of the IUS-12 in ID samples.

Conclusion

In summary, although autism and WS have been commonly conceptualised as developmental disorders which contrast with each other in terms of their social profile, this study shows the importance of understanding the shared mechanisms that may drive atypical emotion regulation in both groups. The evidence here on the role of IU in anxiety and social profile in autism and WS suggests that future research should look at systematically identifying how other factors play a role in the heightened vulnerability for social and anxiety

concerns in autism and WS (e.g. sensory sensitivities and cognitive inflexibility). Cross-syndrome comparison is a really useful way to do this, as it is becoming clear that much is to be gained from understanding of shared mechanisms between these developmental disorders in terms of theory and treatment.

Compliance with Ethical Standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

Asada, K., & Itakura, S. (2012). Social phenotypes of autism spectrum disorders and williams syndrome: Similarities and differences. *Frontiers in Psychology*, *3*, 247. https://doi.org/10.3389/fpsyg.2012.00247

Barak, B., & Feng, G. (2016). Neurobiology of social behavior abnormalities in autism and Williams syndrome. *Nature Neuroscience*, *19*(6), 647–655. https://doi.org/10.1038/nn.4276

Bomyea, J., Ramsawh, H., Ball, T. M., Taylor, C. T., Paulus, M. P., Lang, A. J., & Stein, M. B. (2015). Intolerance of uncertainty as a mediator of reductions in worry in a cognitive behavioral treatment program for generalized anxiety disorder. *Journal of Anxiety Disorders*, *33*, 90–94. https://doi.org/10.1016/j.janxdis.2015.05.004

Bos, D. J., Silverman, M. R., Ajodan, E. L., Martin, C., Silver, B. M., Brouwer, G. J., Di Martino, A., & Jones, R. M. (2019). Rigidity coincides with reduced cognitive control to affective cues in children with autism. *Journal of Abnormal Psychology*, *128*(5), 431–441. https://doi.org/10.1037/abn0000423

Boulter, C., Freeston, M., South, M., & Rodgers, J. (2014). Intolerance of uncertainty as a framework for understanding anxiety in children and adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *44*(6), 1391–1402. https://doi.org/10.1007/s10803-013-2001-x

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007

Comer, J. S., Roy, A. K., Furr, J. M., Gotimer, K., Beidas, R. S., Dugas, M. J., & Kendall, P. C. (2009). The Intolerance of Uncertainty Scale for Children: A Psychometric

Evaluation. *Psychological Assessment*, *21*(3), 402–411. https://doi.org/10.1037/a0016719

Constantino, J. N., & Gruber, C. P. (2012). *Social Responsiveness Scale* (2nd ed.). Western Psychological Services.

Dugas, M. J., & Ladouceur, R. (2000). Treatment of GAD. Targeting intolerance of uncertainty in two types of worry. *Behavior Modification*, *24*(5), 635–657. https://doi.org/10.1177/0145445500245002

Dugas, Michel J., Brillon, P., Savard, P., Turcotte, J., Gaudet, A., Ladouceur, R., Leblanc, R., & Gervais, N. J. (2010). A randomized clinical trial of cognitive-behavioral therapy and applied relaxation for adults with generalized anxiety disorder. *Behavior Therapy*, *41*(1), 46–58. https://doi.org/10.1016/j.beth.2008.12.004

Dugas, Michel J., Gagnon, F., Ladouceur, R., & Freeston, M. H. (1998). Generalized anxiety disorder: A preliminary test of a conceptual model. *Behaviour Research and Therapy*, *36*(2), 215–226. https://doi.org/10.1016/S0005-7967(97)00070-3

Dugas, Michel J., Ladouceur, R., Léger, E., Freeston, M. H., Langlois, F., Provencher, M. D., & Boisvert, J.-M. (2003). Group cognitive-behavioral therapy for generalized anxiety disorder: Treatment outcome and long-term follow-up. *Journal of Consulting and Clinical Psychology*, *71*(4), 821–825.

Dugas, Michel J., Savard, P., Gaudet, A., Turcotte, J., Laugesen, N., Robichaud, M., Francis, K., & Koerner, N. (2007). Can the components of a cognitive model predict the severity of generalized anxiety disorder? *Behavior Therapy*, *38*(2), 169–178. https://doi.org/10.1016/j.beth.2006.07.002

Einstein, D. A. (2014). Extension of the Transdiagnostic Model to Focus on Intolerance of Uncertainty: A Review of the Literature and Implications for Treatment. *Clinical Psychology*, *21*(3), 280–300. https://doi.org/10.1111/cpsp.12077

Factor, R. S., Condy, E. E., Farley, J. P., & Scarpa, A. (2016). Brief Report: Insistence on Sameness, Anxiety, and Social Motivation in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *46*(7), 2548–2554. https://doi.org/10.1007/s10803-016-2781-x

Faja, S., & Nelson Darling, L. (2019). Variation in restricted and repetitive behaviors and interests relates to inhibitory control and shifting in children with autism spectrum disorder. *Autism: The International Journal of Research and Practice*, *23*(5), 1262–1272. https://doi.org/10.1177/1362361318804192

Geurts, H. M., Corbett, B., & Solomon, M. (2009). The paradox of cognitive flexibility in autism. *Trends in Cognitive Sciences*, *13*(2), 74–82. https://doi.org/10.1016/j.tics.2008.11.006

Glod, M., Riby, D. M., & Rodgers, J. (2020). Sensory processing profiles and autistic symptoms as predictive factors in autism spectrum disorder and Williams syndrome. *Journal of Intellectual Disability Research: JIDR*, *64*(8), 657–665. https://doi.org/10.1111/jir.12738

Green, S. A., & Ben-Sasson, A. (2010). Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: Is there a causal relationship? *Journal of Autism and Developmental Disorders*, *40*(12), 1495–1504. https://doi.org/10.1007/s10803-010-1007-x

Janes, E., Riby, D. M., & Rodgers, J. (2014). Exploring the prevalence and phenomenology of repetitive behaviours and abnormal sensory processing in children with Williams Syndrome. *Journal Of Intellectual Disability Research: JIDR*, *58*(8), 746–757. https://doi.org/10.1111/jir.12086

Jones, W., Bellugi, U., Lai, Z., Chiles, M., Reilly, J., Lincoln, A., & Adolphs, R. (2000). II. Hypersociability in Williams Syndrome. *Journal of Cognitive Neuroscience*, *12 Suppl 1*, 30–46.

Keefer, A., Kreiser, N. L., Singh, V., Blakeley-Smith, A., Duncan, A., Johnson, C., Klinger, L., Meyer, A., Reaven, J., & Vasa, R. A. (2016). Intolerance of Uncertainty Predicts Anxiety Outcomes Following CBT in Youth with ASD. *Journal Of Autism And Developmental Disorders*.

Kerns, C. M., Roux, A. M., Connell, J. E., & Shattuck, P. T. (2016). Adapting Cognitive Behavioral Techniques to Address Anxiety and Depression in Cognitively Able Emerging Adults on the Autism Spectrum. *Cognitive and Behavioral Practice*, *23*(3), 329–340. https://doi.org/10.1016/j.cbpra.2016.06.002

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*(9), 809–816.

Leekam, S. (2016). Social cognitive impairment and autism: What are we trying to explain? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *371*(1686), 20150082. https://doi.org/10.1098/rstb.2015.0082

Little, K., Riby, D. M., Janes, E., Clark, F., Fleck, R., & Rodgers, J. (2013). Heterogeneity of social approach behaviour in Williams syndrome: The role of response inhibition. *Research in Developmental Disabilities*, *34*(3), 959–967. https://doi.org/10.1016/j.ridd.2012.11.020

Lough, E., Flynn, E., & Riby, D. M. (2016). Personal Space Regulation in Williams Syndrome: The Effect of Familiarity. *Journal Of Autism And Developmental Disorders*, *46*(10), 3207–3215. https://doi.org/10.1007/s10803-016-2864-8

Magiati, I., Lerh, J. W., Hollocks, M. J., Uljarevic, M., Rodgers, J., McConachie, H., Ozsivadjian, A., South, M., Van Hecke, A., Hardan, A., Libove, R., Leekam, S., & Simonoff, E. (n.d.). The measurement properties of the spence children's anxiety scale-parent version in a large international pooled sample of young people with autism spectrum disorder. *Autism Research*, n/a-n/a. https://doi.org/10.1002/aur.1809

Magiati, I., Tay, X. W., & Howlin, P. (2014). Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. *Clinical Psychology Review*, *34*(1), 73–86. https://doi.org/10.1016/j.cpr.2013.11.002

Maisel, M. E., Stephenson, K. G., South, M., Rodgers, J., Freeston, M. H., & Gaigg, S. B. (n.d.). Modeling the Cognitive Mechanisms Linking Autism Symptoms and Anxiety in Adults. *Journal of Abnormal Psychology*.

McGrath, L. M., Oates, J. M., Dai, Y. G., Dodd, H. F., Waxler, J., Clements, C. C., Weill, S., Hoffnagle, A., Anderson, E., MacRae, R., Mullett, J., McDougle, C. J., Pober, B. R., & Smoller, J. W. (2016). Attention Bias to Emotional Faces Varies by IQ and Anxiety in Williams Syndrome. *Journal of Autism and Developmental Disorders*, *46*(6), 2174–2185. https://doi.org/10.1007/s10803-016-2748-y

Mediation (David A. Kenny). (n.d.). Retrieved June 25, 2020, from http://davidakenny.net/cm/mediate.htm

Nauta, M. H., Scholing, A., Rapee, R. M., Abbott, M., Spence, S. H., & Waters, A. (2004). A parent-report measure of children's anxiety: Psychometric properties and comparison with child-report in a clinic and normal sample. *Behaviour Research and Therapy*, *42*(7), 813–839. https://doi.org/10.1016/S0005-7967(03)00200-6

Ng-Cordell, E., Hanley, M., Kelly, A., & Riby, D. M. (2018). Anxiety in Williams Syndrome: The Role of Social Behaviour, Executive Functions and Change Over

Time. *Journal of Autism and Developmental Disorders*, *48*(3), 796–808. https://doi.org/10.1007/s10803-017-3357-0

Reaven, J., Moody, E. J., Grofer Klinger, L., Keefer, A., Duncan, A., O'Kelley, S., Meyer, A., Hepburn, S., & Blakeley-Smith, A. (2018). Training clinicians to deliver group CBT to manage anxiety in youth with ASD: Results of a multisite trial. *Journal of Consulting and Clinical Psychology*, *86*(3), 205–217. https://doi.org/10.1037/ccp0000285

Riby, D. M., & Hancock, P. J. B. (2008). Viewing it differently: Social scene perception in Williams syndrome and Autism. *Neuropsychologia*, *46*(11), 2855–2860. https://doi.org/10.1016/j.neuropsychologia.2008.05.003

Riby, D. M., & Hancock, P. J. B. (2009). Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders*, *39*(3), 421–431. https://doi.org/10.1007/s10803-008-0641-z

Riby, D. M., Hanley, M., Kirk, H., Clark, F., Little, K., Fleck, R., Janes, E., Kelso, L., O'Kane, F., Cole-Fletcher, R., Allday, M. H., Hocking, D., Cornish, K., & Rodgers, J. (2014). The interplay between anxiety and social functioning in williams syndrome. *Journal of Autism and Developmental Disorders*, *44*(5), 1220–1229. https://doi.org/10.1007/s10803-013-1984-7

Riby, D. M., Janes, E., & Rodgers, J. (2013). Brief report: Exploring the relationship between sensory processing and repetitive behaviours in Williams Syndrome. *Journal Of Autism And Developmental Disorders*, *43*(2), 478–482. https://doi.org/10.1007/s10803-012-1557-1

Riby, D. M., Ridley, E., Lough, E., & Hanley, M. (2017). Chapter Six - Social Vulnerability in Williams Syndrome: A Tendency to Approach Strangers. In M. H. Fisher (Ed.),

International Review of Research in Developmental Disabilities (Vol. 52, pp. 175–199). Academic Press. https://doi.org/10.1016/bs.irrdd.2017.05.001

Rodgers, J., Hodgson, A., Shields, K., Wright, C., Honey, E., & Freeston, M. (2016). Towards a Treatment for Intolerance of Uncertainty in Young People with Autism Spectrum Disorder: Development of the Coping with Uncertainty in Everyday Situations (CUES©) Programme. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-2924-0

Rodgers, J., Riby, D. M., Janes, E., Connolly, B., & McConachie, H. (2012). Anxiety and repetitive behaviours in autism spectrum disorders and williams syndrome: A cross-syndrome comparison. *Journal of Autism and Developmental Disorders*, *42*(2), 175–180. https://doi.org/10.1007/s10803-011-1225-x

Rodgers, J., Wigham, S., McConachie, H., Freeston, M., Honey, E., & Parr, J. R. (2016). Development of the anxiety scale for children with autism spectrum disorder (ASC-ASD). *Autism Research*, n/a-n/a. https://doi.org/10.1002/aur.1603

Royston, R., Howlin, P., Waite, J., & Oliver, C. (2016). Anxiety Disorders in Williams Syndrome Contrasted with Intellectual Disability and the General Population: A Systematic Review and Meta-Analysis. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-2909-z

Sáez-Suanes, G. P., García-Villamisar, D., del Pozo Armentia, A., & Dattilo, J. (2020). Emotional dysregulation and uncertainty intolerance as transdiagnostic mediators of anxiety in adults with autism spectrum disorders and intellectual disability. *Research in Developmental Disabilities*, *106*, 103784. https://doi.org/10.1016/j.ridd.2020.103784

Schmitt, L. M., Bojanek, E., White, S. P., Ragozzino, M. E., Cook, E. H., Sweeney, J. A., & Mosconi, M. W. (2019). Familiality of behavioral flexibility and response inhibition

deficits in autism spectrum disorder (ASD). *Molecular Autism*, *10*. https://doi.org/10.1186/s13229-019-0296-y

Searcy, Y. M., Lincoln, A. J., Rose, F. E., Klima, E. S., Bavar, N., & Korenberg, J. R. (2004). The relationship between age and IQ in adults with Williams syndrome. *American Journal of Mental Retardation: AJMR*, *109*(3), 231–236. https://doi.org/10.1352/0895-8017(2004)109<231:TRBAAI>2.0.CO;2

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(8), 921–929. psyh.

South, M., Beck, J. S., Lundwall, R., Christensen, M., Cutrer, E. A., Gabrielsen, T. P., Cox, J. C., & Lundwall, R. A. (2019). Unrelenting Depression and Suicidality in Women with Autistic Traits. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-019-04324-2

South, Mikle, Carr, A. W., Stephenson, K. G., Maisel, M. E., & Cox, J. C. (2017). Symptom overlap on the srs-2 adult self-report between adults with asd and adults with high anxiety. *Autism Research: Official Journal of the International Society for Autism Research*, *10*(7), 1215–1220. https://doi.org/10.1002/aur.1764

South, Mikle, & Rodgers, J. (2017). Sensory, Emotional and Cognitive Contributions to Anxiety in Autism Spectrum Disorders. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00020

Spain, D., Sin, J., Linder, K. B., McMahon, J., & Happé, F. (2018). Social anxiety in autism spectrum disorder: A systematic review. *Research in Autism Spectrum Disorders*, *52*, 51–68. https://doi.org/10.1016/j.rasd.2018.04.007

Spence, S. H. (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy*, *36*(5), 545–566. psyh.

Spence, S. H., Barrett, P. M., & Turner, C. M. (2003). Psychometric properties of the Spence Children's Anxiety Scale with young adolescents. *Journal of Anxiety Disorders*, *17*(6), 605–625.

Stephenson, K. G., Quintin, E. M., & South, M. (2016). Age-Related Differences in Response to Music-Evoked Emotion Among Children and Adolescents with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *46*(4), 1142–1151. https://doi.org/10.1007/s10803-015-2624-1

Stinton, C., Tomlinson, K., & Estes, Z. (2012). Examining reports of mental health in adults with Williams syndrome. *Research in Developmental Disabilities*, *33*(1), 144–152. https://doi.org/10.1016/j.ridd.2011.09.002

Swain, D., Scarpa, A., White, S., & Laugeson, E. (2015). Emotion Dysregulation and Anxiety in Adults with ASD: Does Social Motivation Play a Role? *Journal of Autism and Developmental Disorders*, *45*(12), 3971–3977. https://doi.org/10.1007/s10803-015-2567-6

Tager-Flusberg, H., & Sullivan, K. (2000). A componential view of theory of mind: Evidence from Williams syndrome. *Cognition*, *76*(1), 59–90.

Tager-Flusberg, Helen, Skwerer, D. P., & Joseph, R. M. (2006). Model syndromes for investigating social cognitive and affective neuroscience: A comparison of autism and Williams syndrome. *Social Cognitive and Affective Neuroscience*, *1*(3), 175–182. https://doi.org/10.1093/scan/nsl035

Top Jr., D. N., Stephenson, K. G., Doxey, C. R., Crowley, M. J., Kirwan, C. B., & South, M. (2016). Atypical amygdala response to fear conditioning in autism spectrum disorder.

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. https://doi.org/10.1016/j.bpsc.2016.01.008

Uljarević, M., Labuschagne, I., Bobin, R., Atkinson, A., & Hocking, D. R. (2018). Brief Report: The Impact of Sensory Hypersensitivity and Intolerance of Uncertainty on Anxiety in Williams Syndrome. *Journal of Autism and Developmental Disorders*, *48*(11), 3958–3964. https://doi.org/10.1007/s10803-018-3631-9

Vasa, R. A., Kreiser, N. L., Keefer, A., Singh, V., & Mostofsky, S. H. (2018). Relationships between autism spectrum disorder and intolerance of uncertainty. *Autism Research: Official Journal of the International Society for Autism Research*, *11*(4), 636–644. https://doi.org/10.1002/aur.1916

Vivanti, G., Hocking, D. R., Fanning, P., & Dissanayake, C. (2016). Social affiliation motives modulate spontaneous learning in Williams syndrome but not in autism. *Molecular Autism*, *7*, 40. https://doi.org/10.1186/s13229-016-0101-0

Walker, S. (2009). *What do we know about the relationship between intolerance of uncertainty and worry in young children?* Newcastle University.

White, S. W., Mazefsky, C. A., Dichter, G. S., Chiu, P. H., Richey, J. A., & Ollendick, T. H. (2014). Social-cognitive, physiological, and neural mechanisms underlying emotion regulation impairments: Understanding anxiety in autism spectrum disorder. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, *39*, 22–36. https://doi.org/10.1016/j.ijdevneu.2014.05.012

Wigham, S., Rodgers, J., South, M., McConachie, H., & Freeston, M. (2014). The Interplay Between Sensory Processing Abnormalities, Intolerance of Uncertainty, Anxiety and Restricted and Repetitive Behaviours in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-014-2248-x

Wood, J. J., Ehrenreich-May, J., Alessandri, M., Fujii, C., Renno, P., Laugeson, E., Piacentini, J. C., De Nadai, A. S., Arnold, E., Lewin, A. B., Murphy, T. K., & Storch, E. A. (2015). Cognitive behavioral therapy for early adolescents with autism spectrum disorders and clinical anxiety: A randomized, controlled trial. *Behavior Therapy*, *46*(1), 7–19. https://doi.org/10.1016/j.beth.2014.01.002

Table 1: Descriptive data and group differences for all measures

	Autism Raw: *M* (SD); [*T*]	WS Raw: *M* (SD); [*T*]	Autism > WS *p*
SRS-2 Total	124.05 (26.27); [≥90]	82.77 (21.30); [73]	.000
SCI	97.02 (21.65); [87]	63.63 (16.95); [70]	.000
RBI	24.79 (7.04); [≥90]	18.38 (6.63); [78]	.000
SCAS-P Total	40.94 (19.77); [60]	24.62 (13.72); [51]	.000
Panic	6.52 (5.31); [60]	3.21 (3.88); [50]	.001
Separation	7.79 (4.30); [63]	5.35 (3.11); [56]	.003
Physical	5.86 (3.48); [64]	4.35 (2.16); [58]	.015
Social	8.48 (4.75); [60]	3.50 (3.01); [45]	.000
OCD	5.79 (4.13); [53]	3.06 (3.10); [44]	.001
GAD	6.88 (4.12); [57]	5.23 (3.09); [50]	.033
IUS-12 Total	41.60 (12.02)	27.42 (11.78)	.000

Note. SRS-2 = Social Responsiveness Scale, 2nd Edition, including Social Communication Index (SCI) and Repetitive, Restricted Behaviors and Interests (RBI) scales. SCAS-P = Spence Children's Anxiety Scales, Parent Report. IUS-12 = Intolerance of Uncertainty Scale for Children, Parent Report 12 Item form.

Caution is indicated for interpretating too strongly any of the SRS-2 individual subscales as these lack evidence for reliability and validity (Constantino & Gruber, 2012; Rodgers et al., 2012; South et al., 2017).

Table 2: Correlations between social profile, anxiety, and IU

	Autism		Williams Syndrome	
	SCAS	IUS-12	SCAS	IUS-12
SRS-2	.45**	.66**	.63**	.73**
SCAS	--	.64**	--	.80**

Note. SRS-2 = Social Responsiveness Scale, Second Edition; SCAS = Spence Children's Anxiety Scale-Parent Report; IUS-12 = Intolerance of Uncertainty Scale for Children, Parent Report 12 Item form

Figure Caption Sheet

Figure 1. Descriptive values for each measure, including markers of cut-scores for clinical concern with the exception of IUS-12, which does not have such a score published, and including neurotypical comparison data from Stephenson et al. (2016). SRS-2 = Social Responsiveness Scale, Second Edition, raw scores; SCAS = Spence Children's Anxiety Scale; IUS-12 = Intolerance of Uncertainty Scale (Short Form). The autism group scored significantly higher ($p < .001$) than the WS group on all measures.

Figure 2 Mediation analysis describing the influence of intolerance of uncertainty on the association between social profiles and anxiety. All parameter coefficients reported are standardized. (*** $p < .001$). 2a: Autism sample. 2b: Williams Syndrome sample

Supplemental Figure 1. Mediation analysis with the mediator and outcome variables interchanged, describing the influence of anxiety on the association between social profiles and intolerance of uncertainty. All parameter coefficients reported are standardized. (*** $p < .001$). S1a: Autism sample S1b: Williams Syndrome sample.

Supplemental Figure 2 Mediation analysis describing the influence of intolerance of uncertainty on the association between social profiles and anxiety only for children 8 years and older. All parameter coefficients reported are standardized. (*** $p < .001$). S2a: Autism sample S2b: Williams Syndrome sample.

Supplemental Figure 3. Mediation analysis with the mediator and outcome variables interchanged, describing the influence of anxiety on the association between social

profiles and intolerance of uncertainty, only for children 8 years and older. All parameter coefficients reported are standardized. (*** $p < .001$). S3a: Autism sample S3b: Williams Syndrome sample.